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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/026835	13.08.2004	13.08.2003

International Patent Classification (IPC) or both national classification and IPC
G06F19/00

Applicant
ICONIX PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/026835

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14,16
	No:	Claims	15,17-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 Reference is made to the following documents:

D1: BHATTACHARYYA C ET AL: "Simultaneous classification and relevant feature identification in high-dimensional spaces: application to molecular profiling data" SIGNAL PROCESSING, AMSTERDAM, NL, vol. 83, no. 4, April 2003, pages 729-743, XP004410718 ISSN: 0165-1684.

D2 : WO 02/10453 A (GENE LOGIC, INC; MENDRICK, DONNA; PORTER, MARK, W; JOHNSON, KORY, R; C) 7 February 2002.

D3: GOLDFARB D ET AL: "Robust convex quadratically constrained programs" MATHEMATICAL PROGRAMMING, vol. 97, no. 3, 1 August 2003, pages 495-515, XP002330564.

2 INDEPENDENT CLAIM 1

2.1 The subject-matter of claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

2.2 D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses (the references in parentheses applying to this document):

A method of identifying a biological state of a biological sample of interest (abstract; page 729, col. 1, par. 1 - page 730, col. 1, par. 2; biological states might be having a disease or not, having certain types of tumour and the like), comprising:

providing a plurality of gene expression datasets associated with a first class of biological samples having a first biological state (page 731, col. 2, par. 4: Two-class data with a number example vectors, associated with a label of +1; page 731, col. 2, par. 1: 46 patients with distant metastases);

providing a plurality of gene expression datasets associated with a second class of biological samples having a second biological state (page 731, col. 2, par. 4:

Two-class data with a number example vectors, associated with a label of -1; page 731, col. 2, par. 1: 51 patients with no distant metastases);

deriving a linear classification rule based on said plurality of gene expression datasets (abstract; page 731, col. 2, par. 5 - page 732, col. 2, par. 1);

and applying said linear classification rule to a set of gene expression levels associated with said biological sample of interest, thereby determining whether said biological sample of interest has said first biological state or said second biological state (page 732, col. 2, par. 1; page 733, col. 2, par. 1- page 734, col. 1, par. 1).

2.3 The subject-matter of claim 1 identifies the biological state of a biological sample as being one of the states of being exposed to a first type of compound or to a second type of compound. Therefore, the difference between the subject-matter of claim 1 and D1 is that the biological states coming from samples exposed to different types of compounds are classified, instead of biological states correspondig to samples taken from diseased or normal tissue types.

2.4 Such a difference cannot be considered as involving an inventive step (Article 33(3) PCT) since microarrays are created to convey the expression profiles corresponding to a variety of conditions and to provide a comparative assessment of many different biological states. In fact, the investigation of the effects of exposure to different compounds is well-known in the art and the comparison of biological states after addition of different compounds is one of the most common uses of microarrays. An example is given by D2 (page 1, line 7- page 3, line 14; page 15, line 30 - page 16, line 25).

2.5 The subject-matter of independent claim 1 thus cannot be considered inventive (Article 33(3) PCT).

3 INDEPENDENT CLAIM 8

3.1 The subject matter of claim 8 does not involve an inventive step in the sense of Article 33(3) PCT.

3.2 The subject-matter of independent claim 8 differs from the disclosure of D1 in that intervals are provided for the gene expression levels in the data sets (see paragraph 2.1.1 above).

3.3 The method of D1 has the disadvantage that it implicitly assumes that the sample vectors used for deriving the linear classification rule are exact. However, as in all experiments, the data generated from the microarray experiments contain errors. Therefore, the classifiers in D1 result in suboptimal decision vectors.

3.4 The problem to be solved by the present invention may therefore be regarded as how to create a robust linear classifier for classifying data sets that are uncertain.

3.5 Faced by this problem, and seeking solution in the appropriate field of optimization, the skilled person would consider D3, which discloses establishing intervals for the data (abstract; page 495, par. 2 - page 496, par. 2, "uncertainty structures of generalized ellipsoids; page 500, par. 3, "confidence regions around the maximum likelihood estimates of parameters"; page 506, par. 2 - page 508, par. 1), and obviously combine these features with what is disclosed in D1 to effortlessly arrive at the subject-matter of claim 8.

3.6 The proposed solution in independent claim 8 thus cannot be considered inventive (Article 33(3) PCT).

4 INDEPENDENT CLAIM 15

4.1 The subject-matter of claim 15 is not new in the sense of Article 33(2) PCT.

4.2 D1 discloses:

A method for classifying a test gene expression dataset (abstract; page 729, col. 1, par. 1 - page 730, col. 1, par. 2) comprising:

providing a reference gene expression dataset (page 730, col. 2, par. 3 - page 731, col. 2, par. 4);

deriving a linear classification rule by reducing the value of a loss function

associated with said reference gene expression dataset (page 731, col. 2, par. 5 - page 733, col. 1, par. 1);

and applying said linear classification rule to a test gene expression dataset thereby determining the classification of the test gene expression dataset (page 733, col. 2, par. 2 - page 734, col. 1, par. 1).

4.3 Therefore, the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT.

5 INDEPENDENT CLAIM 18

5.1 Independent claim 18 defines a computer program product with units corresponding to the steps of method of claim 15. Since the subject matter of claim 15 is not new over the disclosure of D1 and since D1 also discloses a computer program to implement its method (page 732, col. 2, par. 3 - page 733, col. 1, par. 1), the subject-matter of claim 15 is also not new in the sense of Article 33(2) PCT.

6 DEPENDENT CLAIMS 2-7, 9-14, 16, 17, 19

6.1 Dependent claims 2-7, 9-14, 16, 17 and 19 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and inventive step (Article 33(2) and (3) PCT).

6.2 The additional feature of intervals for the expression data defined in claim 2 does not involve an inventive step for the reasons discussed in paragraphs 3.2-3.7 above. It is to be noted that this difference of intervals is not functionally linked to the difference of classification of biological states that result from exposure to different compounds (see paragraphs 2.2-2.5 above). The measurement and statistical errors arise in the data from microarray experiments under all conditions regardless of the type of biological sample tested.

6.3 Referring to claims 3, 4, 10 and 11, D1 discloses deriving a linear classification

function by minimizing a loss function (page 732, col. 1, par. 1 - page 733, col. 1, par. 1). Therefore, the subject-matter of said claims is not inventive.

6.4 Reducing the worse-case of the loss function by taking into account the intervals around the data as in claims 5 and 12 is disclosed in D3 (page 507, par. 4). Therefore, the subject-matter of claims 5 and 12 does not involve an inventive step.

6.5 Identification of a set of classifiers minimizing a loss function as in claims 6 and 13 is disclosed in D1 (page 730, col. 1, par. 2 - col. 2, par. 2; page 732, col. 1, par. 2 - col. 2, par. 3). Therefore, the subject-matter of claims 6 and 13 is not inventive.

6.6 Referring to claims 7, 14, 17 and 19, D1 discloses minimisation of generalisation error for support vector machines and minimax classifiers (page 741, sections A.1 and A.2). Therefore, the subject-matter of claims 17 and 19 is not new and the subject-matter of claims 7 and 14 is not inventive.

6.7 D1 discloses classification of biological states corresponding to normal and diseased conditions (abstract, page 731, col. 2, par. 2 and 3). Therefore, the subject-matter of claim 9 does not involve an inventive step.

6.8 The additional feature of having the expression data set as coming from *in-vivo* compound treatments defined in claim 16 does not involve an inventive step for the reasons discussed in paragraphs 2.2-2.5 above.